REMARKS

I. Status of the Claims

Claims 29 and 30, 32-39, 41, 43-51 and 58 are pending and stand rejected, variously, under 35 U.S.C. §112, first paragraph, §112 second paragraph, 35 U.S.C. §102, and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

All claims stand rejected as lacking written description. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite the modified Int molecules Int-h and Int-h/218. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Objections and Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 34 and 35 are objected to because of the phrase "further comprising, in step (c) ...." An amendment is provided to claims 29, 34 and 35 to address this issue.

Claim 29 is objected to as allegedly encompassing non-elected subject matter. To the extent this is true, claim 29 constitutes a linking claim and should be examined in its entirety upon allowance of elected subject matter.

Claims 49-51 stand rejected under the second paragraph of §112 as indefinite. The amendments to claims 29, 34, and 35, discussed above, as well as that to claim 49, is believed to address the rejection. Also, claim 49 is amended to strike "factor" after "Int."

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejections Under 35 U.S.C. §102

The examiner has rejected claims 29, 30, 32, 33, 41, 44-48 and 51 as anticipated by Lorbach *et al.* Applicants traverse. A copy of translated priority papers is enclosed herewith. Thus, Lorbach *et al.* is not prior art, and reconsideration of the rejection is therefore respectfully requested.

V. Rejections Under 35 U.S.C. §103

A. Hartley *et al.* and Christ & Dröge

Claims 29, 32-35, 41, 44, 45 and 58 stand rejected over Hartley *et al.* and Christ & Dröge. The examiner states that the skilled artisan would have modified the method taught by Hartley *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

In *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown: (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition; and (2) the prior art must have demonstrated a reasonable expectation of success of the invention. The present rejection fails in both these regards.

Hartley *et al.* teach recombinational methods in prokaryotic and eukaryotic host cells using, *inter alia*, the lambda integrase recombination system. However, in contrast to the present invention that uses modified lambda integrases, Hartley *et al.* use exclusively the ***wild-type***

lambda integrase. In contrast, Christ & Dröge, like the present invention, use modified lambda integrases such as Int-h and Int-h/218.

However, ***unlike*** the present invention, Christ & Dröge relates exclusively to integrative and excisive attL/attR and attP/attB recombination performed in ***prokaryotes***, in particular in *E. coli* strains CSH26 and CSH26ΔIHF (see, *e.g.*, p. 825, left col. 2nd sentence; p. 827, right col., "*In vivo* catalytic..." 1st para; p. 829, right col. last para; p. 833/834, M&M "Bacterial strains," "*In vivo* recombination..."). The modified integrases at issue here catalyze recombination in prokaryotes without the need for the co-factors IHF and Xis (see description, p. 14, ll. 13-17; Christ & Dröge, p. 829, left col. 2nd full para, 4th sentence; p.830, right col. 1st para, last sentence).

However, Christ & Dröge does not give the slightest hint that the described modified integrases could also promote recombination events in ***eukaryotic*** cells, to which the present methods are limited. Indeed, the skilled artisan would not contemplate the use of modified integrases in eukaryotic cells for the simple reason that it is well known that the organization of the prokaryotic genome is distinct from eukaryotics. Whereas the prokaryotic genome is circular and condensed due to negative supercoiling and architectural proteins like IHF, the eukaryotic genome is comprised of linear DNA molecules which are highly condensed in nucleosomes by histone proteins. The skilled artisan knows that lambda integrase-mediated recombination is highly dependent on the topological status of the DNA to be recombined and distinct accessory factors. In particular, integrase mediated recombination is dependent on distinct bending specificities of the DNA to allow the formation of DNA/protein complexes which finally give rise to the recombination event (see Christ & Dröge, p. 826, left col., 2nd para to right col. 2nd para). Thus, although the modified integrases of Christ & Dröge, which are adapted to work

without the DNA-stabilizing factor IHF and the enzyme Xis in ***prokaryotic*** cells (*i.e.*, having a ***prokaryotic*** DNA substrate), there was no reasonable basis for the skilled artisan to would also work in ***eukaryotic*** cells, *i.e.*, having a ***eukaryotic*** DNA substrate.

In summary, applicants submit that prokaryotic and eukaryotic DNA properties are fundamentally distinct, so much so that the skilled artisan would not seriously contemplate transferring the modified integrase recombination system of Christ & Dröge to a eukaryotic host organism/cell, and even if they were so motivated, there was no reasonable expectation of success in so doing. Hence, the combination of the teachings of Christ & Dröge with Hartley *et al.* is not *prima facie* obvious. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Crouzet *et al.* and Christ & Dröge

Claims 29, 30, 32, 33, 41, 44-48 and 48 are rejected over the combined disclosures of Crouzet *et al.* and Christ & Dröge. The examiner states that the skilled artisan would have modified the method taught by Crouzet *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

Just as with the rejection above based on Hartley *et al.*, applicants submit that the rejection here is flawed as well. This is, again, due to the simple fact that Crouzet *et al.* worked with wild-type integrases, and Christ & Dröge worked in prokaryotic systems. There was no motivation for combining these two very distinct systems, and even if there were, there was no likelihood of success that they would be compatible, *i.e.*, that the modified integrases of Christ &

Dröge would function in a eukaryotic system. Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

C. Crouzet *et al.*, Christ & Dröge, and Capecchi *et al.*

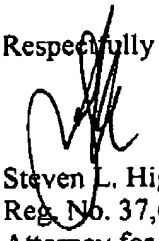
Claims 29 and 43 are rejected over Crouzet *et al.*, Christ & Dröge and Capecchi *et al.* Applicants traverse.

Just as with the previous rejections, applicants submit that the rejection here fails for lack of motivation and lack of an expectation of success. The defects of Crouzet *et al.* and Christ & Dröge have been discussed above and will not be repeated here. Capecchi *et al.* fails to address the issue of whether modified integrases would work in eukaryotic cells. Thus, again, there was no motivation for combining the primary and secondary references, and even if there were, there was no likelihood of success that they would work together. Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

VI. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should the examiner have any questions regarding the content of this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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